

10/530139

CLAIMS

JC13 Rec'd PCT/PTO 04 APR 2005

1. A process for the preparation of 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-5(10)-en-20-yn-3-one of formula 1, which comprises:

5 (a) hydrolyzing 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-5(10)-en-20-yne 3,3-cyclic ketals of formula 2, where:

(1) each of R₁, R₂, R₃ and R₄ is a hydrogen atom or a C₁₋₄ alkyl group, or

10 (2) R₁ and R₃ are taken together to form an alicyclic ring together with the carbon atoms in the dioxolane ring to which the groups are attached and R₂, R₄ are hydrogen atoms, or

15 (3) R₁ and R₃ are taken together to form an aromatic ring together with the carbon atoms in the dioxolane ring to which they are attached, and R₂, R₄ are taken together to form a chemical bond participating in the aromatic electron system of the aromatic ring formed by R₁ and R₃;

20 in the presence of salts of transition metals, salts of lithium or salts of magnesium;

(b) separating 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-5(10)-en-20-yn-3-one obtained in step (a) from 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-4-en-20-yn-3-one by-product of formula 3; and

25 (c) converting 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-4-en-20-yn-3-one obtained as a by-product in step (b)

to the ketal of formula 2, wherein R₁-R₄ are defined as above, which is then hydrolyzed to 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-5(10)-en-20-yn-3-one in step (a).

- 5 2. A process according to claim 1, which in step (a) comprises hydrolyzing 3,3-ethylenedioxy-17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-5(10)-en-20-yne.
3. A process according to claim 2, characterized in that 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-5(10)-en-20-yn-3-one is obtained in a molar excess to 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-4-en-20-yn-3-one equal at least 4:1.
- 10 4. A process according to claim 3, characterized in that 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-5(10)-en-20-yn-3-one is obtained in a molar excess to 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-4-en-20-yn-3-one equal at least 8:1.
- 15 5. A process according to claim 1, where the metal salt used in step (a) is copper(II) sulfate.
6. A process according to claims 1-5, characterized in that the hydrolysis reaction is carried out in a mixture of solvents containing 0%-99% water, 0%-100% of an organic solvent selected from a group consisting of THF, CHCl₃, 1,4-dioxane, CH₂Cl₂, acetone, acetonitrile, ethylmethylketone, diethylketone, 1,3-dioxolane, 1,2-dimethoxyethane, 1,2-diethoxyethane, and 0%-100% of a C₁₋₄ alcohol.
- 20 25 7. A process according to claims 1-6, where the reaction temperature is from about 0°C to about 200°C.

8. A process according to claim 1, characterized in that 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-4-en-20-yn-3-one of formula 3 is in step (c) converted to a 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-5(10)-en-20-yne 3,3-ketal of formula 2 by reaction with a vicinal diol of the formula R₁R₂C(OH)-C(OH)R₃R₄, in the presence of a protic acid and a hydrocarbon solvent.
9. A process according to claims 1 and 8, characterized in that the 17 β -hydroxy-7 α -methyl-19-nor-17 α -pregn-5(10)-en-20-yne 3,3-ketal of formula 2, obtained in step (c), is substantially purified before the hydrolysis step (a), by crystallization from a mixture of organic solvents containing 50%-100% ethyl acetate.

BEST AVAILABLE COPY